

A revision of the El Escorial criteria - 2015

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Introduction

There has been much discussion as to the necessity for adjustment of the El Escorial diagnostic criteria, primarily based on observations relating to the specificity of the 'Possible' category. The WFN subgroup on ALS/MND has initiated a process of consultation pertaining to the undertaken wider domains of ALS clinical phenotype, the results of which have been published recently (1). Subsequent to this, the WFN Research Group on ALS/MND has developed a document pertaining to the classification of amyotrophic lateral sclerosis, which was posted online for general comment from January to April 2014 and again between January and March 2015. We now outline a summary of the discussions with respect to El Escorial classification system for ALS.

Diagnostic criteria

The diagnosis of ALS is based on the exclusion of alternative causes of signs and symptoms as outlined in the original diagnostic criteria (1). Assuming that such an evaluation has occurred, ALS also requires clinical progression. With respect to specific signs at the time of diagnosis, we propose that the diagnosis of ALS requires, at minimum, one of the following:

- progressive upper and lower motor neuron deficits in at least one limb or region of the human body; i.e. meeting the revised El Escorial criteria for possible ALS.
- or
- lower motor neuron deficits as defined by clinical examination (one region) and/or by EMG in two body regions (defined as bulbar, cervical, thoracic, lumbosacral). The EMG findings consist of neurogenic potentials and fibrillation potentials and/or sharp waves.

Restricted phenotypes of ALS currently recognized include:

1. Progressive bulbar palsy (PBP)
 2. Flail arm (Vulpian Bernhard) syndrome and Flail leg syndrome
 3. Progressive muscular atrophy (PMA)
 4. Primary lateral sclerosis (PLS)
1. Progressive bulbar palsy is a progressive motor neuron disease that affects only the muscles supplied by bulbar motor nuclei and the corticobulbar pathways. To the extent that both upper and lower motor neuron deficits are discerned, ALS can be diagnosed as above.
 2. Flail arm syndrome (Vulpian Bernhard syndrome) and Flail leg syndrome begin with asymmetric deficits of the arms or legs. When these syndromes involve at least two body regions, ALS can be diagnosed in the absence of clear UMN signs (see above).
 3. Progressive muscular atrophy is diagnosed if there is clinical evidence of lower motor neuron disease in one limb or region and clinical or electrophysiological evidence of involvement of an adjacent limb or region. When this syndrome involves at least two body regions, ALS can be diagnosed in the absence of clear UMN signs (see above), assuming that appropriate genetic testing is performed to rule out other specific motor neuron diseases.
 4. Primary lateral sclerosis is a syndrome in which the disease begins with upper motor neuron deficits existing in isolation. As such, ALS cannot be diagnosed. If and when clinical or electrophysiological evidence of involvement of the lower motor neuron in at least one limb or body region is present, ALS can be diagnosed (see above).

Hereditary ALS is considered if at least one first or second degree relative suffers from ALS and/or frontotemporal dementia (FTD). If a positive family history for either ALS or FTD within three generations is documented, the term FALS should be used. If a pathogenic mutation in a disease-causing gene is found in the patient and segregates with the disease the term hereditary or primary genetic ALS (HALS/GALS) should be used. The finding of a pathogenic mutation in a known gene can substitute for either lower or upper motor neuron signs, so that diagnosis of ALS can be made on the basis of UMN or LMN signs in one body region, associated with a positive genetic test.

Principal decision

A diagnosis of ALS can be made if the former criteria for 'possible ALS' are fulfilled. This is based on extensive data from natural history studies and ALS clinical trials showing that the false-positive rate is not appreciably higher for possible ALS, and imaging and pathological literature suggesting that UMN pathology is present in cases when only lower motor neuron signs are appreciated clinically. It can thus be concluded that more widespread LMN disease (i.e. two or more body regions) in the absence of UMN signs or any other explanation for the LMN clinical signs is sufficient for the diagnosis of ALS. This opens the opportunity that restricted phenotypes of ALS can be included in the diagnosis and, where appropriate, enrolled in clinical trials.

The following data are presented in support of the decision:

- In those clinical trials that used the inclusion criterion of 'possible ALS' only, a negligible number of wrong diagnoses were observed at follow-up.
- During recent decades a number of methods have appeared (MRI, CSF examinations) that identify other causes of upper motor neuron signs, which are of differential diagnostic importance (such as cervical myelopathy and myelitis). These methods are now routine procedures in the majority of clinical settings.

Staging of ALS

The former categories of probable and definite ALS should be replaced by a new and validated staging system. The development of other non-invasive investigations, including MRI, that reliably define and quantify upper motor neuron deficits in the individual patient will also assist in staging.

Cognitive impairment

As cognitive impairment is an integral part of up to 50% of those with ALS, the presence of dementia

(FTD, AD) does not exclude the diagnosis of ALS. Any new staging system should include a cognitive domain.

Concomitant signs

Deficits in sensory, oculomotor systems and sphincter disturbances can be features of ALS.

EMG findings

EMG findings that occur in the presence of ALS include neurogenic potentials, fibrillation potentials, positive sharp waves, and fasciculation potentials. Diagnostic sensitivity is increased by the substitution of fasciculation potentials for fibrillation potentials. However, it must be recognized that the origins of fasciculations are multiple, and are not always representative of lower motor neuron disease.

Restricted phenotypes

PBP develops into disseminated ALS; this is also true for Flail arm (Vulpián-Bernhard variant) and Flail leg syndromes. PMA is seen as a subform of ALS, as there is clear evidence in the literature that this syndrome is associated with upper motor neuron disease post mortem in the majority of patients. Also, several patients with a PMA phenotype have been found to carry known pathogenic ALS mutations. In the vast majority of patients, PLS develops into ALS; restricted phenotypes may have a different prognosis from the more common disease forms and retention of this subcategory is therefore desirable.

Genetics

Familial ALS is not the same as hereditary ALS. Accordingly, the term hereditary ALS should be considered if a first- or second-degree relative suffers from ALS or FTD. ALS can be defined as Mendelian in inheritance if a disease-causing gene variant can be shown to segregate within a family. In such cases the genetic variant gene can serve as a substitute for upper motor neuron deficits or a second limb or region ('rule of two').

Acknowledgements

We devote this paper to Imaharu Nakano who died in July 2014, shortly before we finished the process of discussing and establishing the new diagnostic criteria.

Reference

1. Agosta F, Al-Chalabi A, Filippi M, Hardiman O, Kaji R, Meininger V, et al., for the WFN Research Group on ALS. The El Escorial Criteria: Strengths and Weaknesses. *Amyotroph Lateral Scler Frontotemporal Degener.* (2014), in press.